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MEDICAL STAFF CONFERENCE

Combinations of Antimicrobials

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* We are very pleased to have Dr. Ernest Jawetz with us today to discuss the rationale for the use of combination of antibiotics.

DR. JAWETZ:† On the whole, physicians are well satisfied with the position of antimicrobial drugs. They derive a feeling of security from the fact that a majority of microbial infections can be treated effectively and cheaply and that most patients recover not only from the infection but also from the undesirable effects of the drugs. However, from time to time, the physician's feeling of security is threatened. He hears about the emergence of drug resistance, about superinfections, about failures of antimicrobial drug treatment. At such times he wonders: If one drug is good, might two not be better, and might three not cure every patient of every disorder? Such sentiments are undoubtedly involved in the very widespread use of antimicrobial combinations. For example, 11 percent of 7,094 patients admitted to Johns Hopkins Hospital during a three-month period in 1963 received from two to five antibiotics, whereas only an additional 7 percent received a single antibiotic. Some years ago a correspondent, surveying the German drug market, found hundreds of preparations containing several drugs and concluded: "It has become unfashionable to use one drug by itself."[1,2]

Even if we acknowledge the vast abuse of drug mixtures, some reasonable indications for the use of antimicrobials in combinations may be listed briefly:

1. Prompt treatment of a desperately ill patient who is suspected of having a serious infection. Two or more drugs are aimed at the several most likely pathogens. The commonest example at present is the initial treatment of suspected Gram-negative bacterial sepsis. Commonly employed combinations "aimed" at the most serious organisms consist of gentamicin plus carbenicillin, or kanamycin plus cephalothin or ampicillin.

2. The emergence of microbial mutants resistant to one drug may be greatly delayed by the simultaneous presence of a non-cross reacting second drug. This applies particularly to chronic infections—for example, tuberculosis where simultaneous use of two drugs, or even three drugs, is universally accepted to deal with large microbial populations in symptomatic disease.

3. Mixed infections—for example, in the respiratory tract—usually are well managed with a single drug. Very rarely, however, simultaneous sepsis with two organisms may require the use of two drugs, each aimed at one organism.

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4. The desire to achieve bactericidal synergism is a much advertised claim and a fervent desire —but very rare in reality. It is discussed below.

In contract to the above list of possible clinical indications for antimicrobial combinations, there is a longer list of disadvantages of their use:

1. If a physician already administers penicillin, kanamycin, erythromycin, tetracycline, cephalothin, vancomycin—and a dash of cortisone—to a very sick patient, he feels that everything possible is being done for that patient. This gives the physician a false sense of security, and he will not expend all possible effort toward a specific diagnosis which might permit specific treatment. The result is direct harm to the patient.

2. The more antimicrobials given simultaneously, the greater the chance for sensitization of the patient, or for adverse reactions, be they toxic or hypersensitive.

3. Unnecessarily high cost.

4. All too frequently a drug combination achieves no greater therapeutic benefit than a properly selected, effective single drug.

5. "Fixed" antimicrobial combinations are always unsuitable for specific treatment; usually there is too high a dose of one drug and too low a dose of the other drug. This and many other reasons have led to the recent disapproval of fixed antimicrobial combinations by regulatory agencies in the United States.

Let us now review the types of combined drug effects which might occur if two antimicrobials act simultaneously on a homogeneous microbial population (Chart 1). By far the commonest situation is that drug A has very little effect, and drug B is moderately effective in reducing the number of viable microorganisms. A plus B is similar to B (the more active drug) alone. This type might be called "indifference of drug interaction," and it occurs in a large majority of clinical situations where two antimicrobials are employed together—a striking waste.

The most desirable interaction might be called "synergism": Drug A alone has very little effect, drug B inhibits growth moderately, but—through some magic—A plus B produces rapid killing of the entire microbial population. Such "synergism" unfortunately is very rare, and it is entirely specific for a given drug combination, acting on a single strain of microbes.

The third possibility is that drug A alone is significantly bactericidal against an organism,

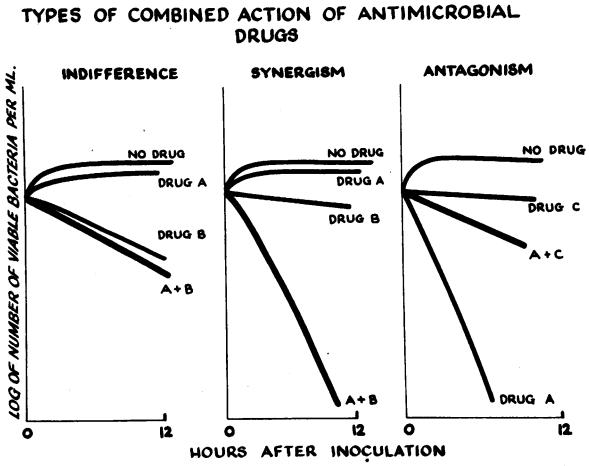

Chart 1.—Types of combined action of two antimicrobial drugs on a homogeneous microbial population. Schematic representation of bactericidal action *in vitro*, showing the possible types of results seen when one drug, or two drugs, act on a homogeneous population of bacteria, under conditions permitting growth.

while drug C alone has a barely inhibitory effect. The addition of C to A results in a pronounced reduction of the antibacterial efficacy of A. This can be called "antagonism." A few characteristics of antimicrobial antagonism are worth noting. *In vitro* antagonism is observed most readily as a reduction in the rate of bactericidal action when two drugs are acting simultaneously on a homogeneous microbial population. In experimental infections (Chart 2), this antagonism can also be demonstrated when a primarily bacteriostatic agent (for example, chloramphenicol, tetracycline, sulfonamide) in a barely effective amount is administered before, or with, a minimal therapeutic dose of a bactericidal agent (for example, a penicillin, an aminoglycoside). However, the antagonism can be overcome readily by an excess of the bactericidal drug (Chart 2). The mechanism of antagonism is not fully understood, but it apparently depends on a pronounced slowing of microbial metabolism by the "antagonizing" drug (for example, an inhibitor of protein synthesis) before the action of the bactericidal drug (for example, an inhibitor of cell wall synthesis) if the latter depends on active microbial metabolism for optimal action. The experimental demonstration of antimicrobial antagonism *in vitro* and *in vivo* is interesting—but does antagonism ever occur in clinical treatment of human infections? It can occur under special circumstances. The best known examples

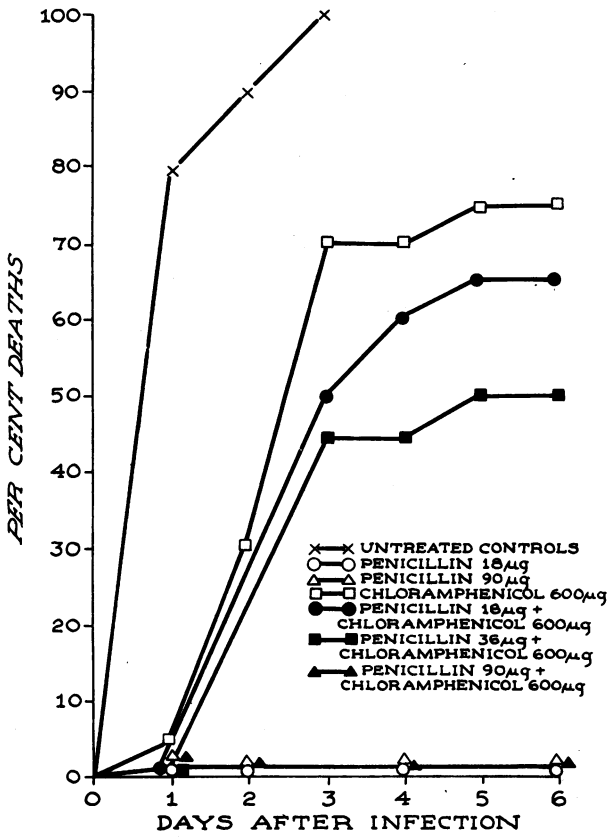

Chart 2.—Death rates observed in a streptococcal infection of mice treated with penicillin alone (18 or 90 μg per mouse), chloramphenicol alone (600 μg per mouse), or penicillin in various doses administered at the same time as chloramphenicol, but injected separately. While chloramphenicol antagonizes the action of penicillin, an excess of penicillin can overcome this antagonism.

come from the treatment of bacterial meningitis. Twenty years ago Lepper and Dowling[3] showed that in the treatment of pneumococcus meningitis the addition of chlortetracycline to full therapeutic doses of penicillin decidedly increased the mortality (Table 1). More recently Mathies et al[4] had a similar experience with the addition of chloramphenicol to therapeutic doses of ampicillin in bacterial meningitis of children (Table 2). While antimicrobial antagonism thus *can* occur in clinical therapy (the literature contains several other examples), I believe that it is so limited by time-dose relationships (see above) as to be an unlikely and rare outcome in the treatment of human infections.

The possibility of achieving synergistic effects deserves detailed discussion. At least three mechanisms for antimicrobial synergism are known.[5]

TABLE 1.—*Clinical antibiotic antagonism. Treatment of pneumococcus meningitis

	No. of Patients	Deaths No.	Deaths Percent
Penicillin 12 million units i.m. daily X 14	43	13	30
Penicillin, same dose + chlortetracycline, 50 mg per kg per day i.v.	14	11	79

*Cases of comparable stage and severity.[3]

TABLE 2.—*Ampicillin in bacterial meningitis*[4]

Drugs Used	No. of Patients	Deaths No.	Deaths Percent
Ampicillin 150 mg per kg per day 10-12 days	140	6	4.3
Ampicillin 150 per mg per kg per day + chloramphenicol 100 mg per kg per day + streptomycin (2 days)	124	13	10.5

1. *Blocking successive steps in a metabolic sequence.* Sulfonamides are antibacterial because they compete with para-amino-benzoic acid which is required by some bacteria for the synthesis of dihydrofolate. Folate antagonists (for example, trimethoprim, pyrimethamine) inhibit the activity of the enzyme which reduces dihydrofolate to tetrahydrofolate (dihydrofolic acid reductase). These folate antagonists inhibit bacterial and protozoal enzyme thousands of times more efficiently than the enzyme of mammalian cells. The simultaneous presence of a sulfonamide and a folate antagonist results in the simultaneous block of sequential steps in the pathway, leading to the synthesis of purines and nucleic acid (Chart 3). Such a simultaneous block can result in much more complete inhibition of growth than the action of either component alone. Optimal proportions of the components of the mixture have been estimated *in vitro,* but may be difficult to maintain *in vivo.* This type of "synergistic," combined antimicrobial action is being applied to urinary tract infections, enteric fevers, malaria, and toxoplasmosis.[6]

2. *Inhibition by one drug of an enzyme which can destroy the second drug.* Penicillins suscep-

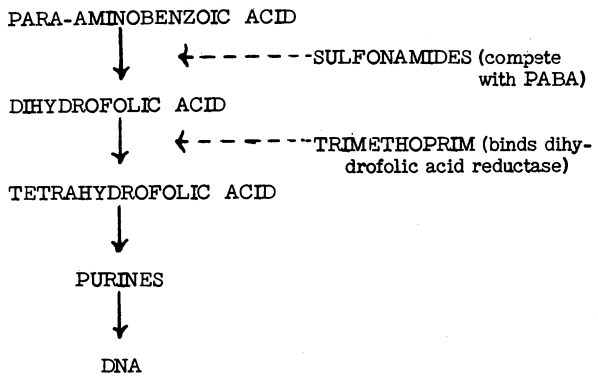

Chart 3.—Mechanism of the synergistic action of a sulfonamide and a folate antagonist.

tible to destruction of beta-lactamases (penicillinases) are usually ineffective against organisms which produce such lactamases. However, if the lactamase of an organism could be firmly bound, then penicillins might be effective against this organism. Certain lactamase-resistant penicillins and cephalosporins have a much higher affinity for some lactamases than do hydrolyzable penicillins (for example, penicillin G, ampicillin). Lactamases from pseudomonas and other Gram-negative bacteria are bound very efficiently by methicillin, cloxacillin or cephalosporins. These drugs are resistant to lactamase action and can protect hydrolyzable penicillins from destruction. This type of synergistic effect has been employed a few times in clinical therapy,[7] but sufficient concentrations of the binding drugs are easily achieved only in urine, not in the systemic circulation.

3. *Synergism manifested by pronounced enhancement of early bactericidal rate.* This type of combined antimicrobial action has been studied extensively and reviewed repeatedly.[5,8] Some of its characteristics are as follows: The effect extends over a fairly wide range of concentrations of each member of the drug pair; only one member of the pair need exhibit antimicrobial activity alone in the concentration employed in the mixture; the other member may be ineffective in that concentration, although active against the particular organism in a 10-fold to 1000-fold higher concentration.

This type of synergism has been demonstrated with Gram-negative bacteria, staphylococci and other organisms, but it has been studied in greatest detail with enterococci (Streptococcus fecalis). Most enterococci are inhibited, but not killed, by penicillins.[8,9] The addition of an aminoglycoside (streptomycin, kanamycin, gentamicin) in amounts achievable in the systemic circulation results in an immediate, striking increase in the rate of bactericidal action, although that concentration of aminoglycoside alone has no discernible effect *in vitro*. Enormous concentrations of a given aminoglycoside (for example, streptomycin 6 mg per ml, kanamycin 3.7 mg per ml) are inhibitory to the enterococcus *in vitro*, unless the particular strain is genetically resistant. In the latter case there will be no synergism when that particular aminoglycoside is added to a penicillin.[10,11] The mechanism of this type of synergism probably depends on the ability of drugs which inhibit cell wall synthesis (for example, penicillin) to greatly enhance the permeability of enterococci to aminoglycosides, so that the latter can exert a lethal action on the ribosomes of the bacteria. The uptake of radioactive aminoglycosides is greatly enhanced in enterococci by penicillins, but not by drugs which affect cell membranes, or protein synthesis.[12] However, cephalosporins do not readily participate in this synergistic effect with aminoglycosides.

Enterococci (Streptococcus fecalis) are the etiological organisms in 5 to 15 percent of cases of bacterial endocarditis. Treatment with penicillin alone fails to cure a majority of patients with enterococcal endocarditis,[9,13] and only a few patients have been treated and cured with ampicillin alone. By contrast, penicillin combined with an aminoglycoside has frequently eradicated the infection. In the past, most commonly, penicillin was given together with streptomycin or kanamycin.[13,14] More recently, some strains have appeared to be completely resistant to huge concentrations of these aminoglycosides,[10,11,15] but still susceptible to a combination of penicillin with gentamicin.[16]

Synergistic combinations of carbenicillin with gentamicin have been employed in pseudomonas sepsis of immunodeficient leukemic patients.[17] Other types of Gram-negative sepsis may also be susceptible to "synergistic" drug action [18,19] if a specific drug combination can be selected by laboratory means for a specific infecting organism. Before the advent of specific anti-staphylococcal penicillinase-resistant drugs (for example, methicillin, vancomycin) cases of staphylococcal endocarditis could often be cured by specifically selected synergistic drug combinations.[20] In many

other claims for the clinical efficacy of "synergistic" antimicrobial combinations, there are serious doubts regarding the validity of the evidence on which the claim is based.

Conclusion

Perhaps because of its large financial impact, the field of combined antimicrobial drug action has been filled with intense emotions, violent claims and counterclaims. An effort was made in this brief summary to describe the simplest common denominators which determine combined antimicrobial activity in the laboratory and in its application to clinical treatment. A famous physician, Moses ben Maimon, is said to have written 800 years ago: "If one can manage well with one individual drug, one should not use a compound one. . . . One should use medications compounded of multiple ingredients only when compelled to do so."[21] I may express the pious hope that my brief presentation may help physicians feel compelled less often to use combinations of antimicrobial drugs.

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FLUID REPLACEMENT IN BURNED PATIENTS

In our studies on fluid replacement in burn patients, I think one thing stands out: The rapidity of fluid loss is much faster than we have been led to believe by replacing fluids according to clinical signs. In essence our studies really show that the majority, if not all, of the fluid sequestration into the burned area is in the first 24 hours. By using a 48-hour period of fluid replacement, we are playing "catch-up." So we attempt, and have been for the last several years, to give the entire quantity in 24 hours, with quite beneficial results. I think also that it's less important what particular solution you choose as long as you give enough of it and fast enough.

—Basil A. Pruitt, Jr., Ft. Sam Houston

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